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Pathologic Features and Patient Survival in Hepatocellular Carcinoma in Relation to Age

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For hepatocellular carcinoma, the peak age of patients is at the sixth decade. However, the influence of age on the tumor biologic behavior and long-term patient survival is controversial. We retrospectively studied 278 patients whose hepatocellular carcinomas were surgically resected to analyze the pathologic and clinical features of the tumors and patient survival in relation to age. The patients were divided into two groups, younger than 50 years of age and older than 50 years. Ninety-seven patients were 50 years of age or under, and 181 were older than 50 years. The younger patients had: (1) more frequent hepatitis B surface antigen positivity ($P = 0.022$), (2) less cirrhosis ($P = 0.050$), (3) less tumor encapsulation, (4) a more advanced tumor stage in terms of more venous permeation ($P = 0.012$), more liver invasion ($P = 0.010$) and larger tumor ($P = 0.002$), and (5) a more frequently raised serum alpha-fetoprotein level ($P = 0.035$). In spite of the more advanced stage of the tumors, both the actuarial and disease-free survival rates did not differ significantly from those of the older group. The operative mortality rates also were similar in both groups. To conclude, there were distinct differences in the clinical and pathologic features of the tumors of patients <50 years and those older. Although the tumors were more advanced in the younger group, the less frequently associated cirrhosis in this group might have partly compensated to result in survival rates similar to those of the older group. Because of the comparable survival rates, the treatment policy in the older group should not differ greatly from that in the younger group.

KEY WORDS: **hepatocellular carcinoma, age, clinicopathologic features, patient survival**

INTRODUCTION

For hepatocellular carcinoma (HCC), surgical resection offers a long-term survival. The contribution of age to long-term survival is, however, controversial. Some reports found that younger patients had a better prognosis than the older ones [1–3], whereas others found that age of the patients was not a prognostic factor in patients with HCC [4–7]. In addition, information on the pathologic features and biologic behavior of the tumors in relation to age is scanty [7]. We therefore analyzed our patients to examine the influence of age on the clinicopathologic features and patient survival.

MATERIALS AND METHODS

Between 1972 and 1993, 278 cases of primary HCC were surgically resected at Queen Mary Hospital, Hong Kong. The pathologic features of the tumors, as well as some clinical features of these patients, were reviewed. The disease recurrence and survival rates of the patients after hepatic resection were analyzed. The presence of

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hepatitis B surface antigen (HBsAg) and serum alpha-fetoprotein (AFP) levels were from well-documented records. The macroscopic and microscopic features of the tumors and the nontumorous livers were assessed and included 19 pathologic parameters. They were: tumor size measured as the maximal diameter of the biggest tumor, gross appearance of the tumor as described by Eggel [8], number of tumor nodules, tumor capsule, capsular invasion, venous permeation, tumor microsatellite formation, direct liver invasion, presence of tumor at the resection margin, cellular differentiation according to Edmondson and Steiner [9], pattern of cellular architecture, presence of clear cells, giant cells and hyaline inclusions, amount of intratumoral stroma and mononuclear cell infiltration, bile production, presence of cirrhosis, and, if present, its activity.

Prior to 1985, postoperative follow-up depended on clinical examination and hepatic angiography when recurrent disease was suspected. Since 1985, all patients have been monitored with a combination of serial serum AFP sampling and percutaneous ultrasonographic examination of the hepatic remnant by the Department of Radiology. Investigations were performed at monthly intervals for the first postoperative year and every 2–4 months thereafter. Whenever possible, disease recurrence was confirmed by biopsy. In the absence of histologic confirmation, the diagnosis of recurrent HCC was based on the elevated serum AFP level and radiologic evidence, or both.

Recurrence of the disease was analyzed without further delineation into intrahepatic or extrahepatic one. Disease-free survival (DFS) was measured from the date of hepatic resection to the date when recurrent disease was diagnosed, or in the absence of detectable tumor, to the date of death or last follow-up. Actuarial survival (AS) was measured from the date of hepatic resection to the date of death. Operative mortality was defined as death within 30 days after hepatectomy.

Fisher's exact and Chi-square tests were used for the analysis of categorical data, whereas correlation analysis, analysis of variance, and the Kruskal-Wallis test were used for continuous data. Survival analysis were performed as described by Kaplan and Meier [10].

RESULTS

Clinical and Pathologic Features

The ages of the patients ranged from 24–79 years (mean ± S.D. being 53.9 ± 12.0 yr). Ninety-seven (34.9%) patients were 50 years of age or under, and 181 >50 years. The mean age of the younger group was 41.1 yr and that for the older group was 64 yr.

Among the 19 pathologic and three clinical parameters (gender, HBsAg status, and serum AFP levels), we found that patients in the younger group were: (1) more frequently HBsAg positive, (2) less frequently cirrhotic, had (3) less tumor encapsulation, (4) a more advanced tumor stage (more venous permeation, more liver invasion, and larger tumor), and (5) a more frequently raised serum AFP level (Table I).

TABLE I. Pathologic Features of Hepatocellular Carcinomas in Relation to Age

Finding	No. of patients (%) ≤50 yr	>50 yr	*P* value
Absence of encapsulation	32 (37.6)	88 (56.1)	0.006
Presence of venous permeation	69 (75.0)	100 (59.5)	0.012
Poorer cellular differentiation (Edmondson's grades III/IV)	33 (37.5)	41 (26.1)	0.063
Presence of liver invasion	57 (69.5)	78 (52.0)	0.010
Positive HBsAg[a]	73 (83.9)	114 (70.8)	0.022
Liver cirrhosis	48 (50.0)	109 (62.3)	0.050
active cirrhosis	12 (25.0)	49 (45.0)	}
inactive cirrhosis	36 (75.0)	60 (55.0)	} 0.034
Microsatellite formation	49 (57.0)	85 (52.8)	NS[c]
Tumor at resection margin	20 (23.8)	31 (20.5)	NS
Serum AFP[b] level > 200 ng/ml	61 (72.6)	90 (58.8)	0.035
Female gender	12 (12.4)	23 (12.7)	NS
Mean tumor size (cm)	10.4	8.4	0.002

[a] Hepatitis B surface antigen.
[b] Alpha-fetoprotein.
[c] NS = not significant.

Of all patients, 74.5% was HBsAg positive. 83.9% of the younger patients were HBsAg positive, whereas 70.8% of the older ones were positive ($P = 0.022$). Significantly fewer (50%) patients of the younger group had histologic evidence of cirrhosis of the liver, compared to 62.3% in the older group ($P = 0.050$). Among those cirrhotic patients, the cirrhosis was substantially more frequently inactive in the younger group (75%), compared with that (55%) in the older one ($P = 0.034$). In addition, significantly fewer patients of the younger group (37.6%) had tumor encapsulation, whereas 56.1% of the patients in the older group had tumor encapsulation ($P = 0.006$). The tumors in the younger group also were more advanced in stage. They more frequently had venous permeation ($P = 0.012$) and tumor invasion of the adjacent livers ($P = 0.010$). In addition, their tumors of the younger group were significantly larger than those of the older group, with a mean diameter of 10.4 cm in the younger one, compared to 8.4 cm in the older one ($P = 0.002$). The tumors also tended to be more poorly differentiated, with 37.5% being of Edmondson grades III to IV, compared with 26.1% in the older group ($P = 0.063$). However, the incidence of tumor microsatellite formation and presence of tumor at resection margins did not differ significantly between these two groups. The other pathologic features studied showed no significant differences between the two groups.

A raised serum AFP level >200 ng/ml was present in 151 (63.7%) of the 237 patients with serum AFP assayed. More patients (72.6%) of the younger group had a raised serum AFP level >200 mg/ml than the older group

TABLE II. Median Actuarial and Disease-Free Survival and Operative Mortality Rates of Patients With Surgically Resected Hepatocellular Carcinoma in Relation to Age

	Patients		
	≤50 yr	>50 yr	*P* value
Median actuarial survival (months)	16.1	15.1	NS[a]
Median disease-free survival (months)	4.3	5.3	NS
Operative mortality rate	7.4%	10.8%	NS

[a]NS = not significant.

(58.8%) ($P = 0.035$). Of these 278 patients, 243 were men and 35 women. In the younger group, 12 (12.4%) patients were female, compared with 23 (12.7%) in the older group. There was no significant difference in the gender between these two groups.

Survival Analyses

The overall median AS and DFS were 23.6 and 9.2 months, respectively. The overall DFS rates at 1, 3 and 5 years were 42%, 23%, and 17%, respectively, and the overall AS rates for the corresponding time periods were 70%, 39%, and 28%, respectively. The median AS and DFS for the younger group were 16.1 and 4.3 months, respectively, and those for the older group 15.1 and 5.3 months, respectively. The differences between the median AS and DFS of the two groups were not statistically significant (Table II).

The operative (30-day) mortality rate for the older group was 10.8%, that for the younger group was 7.4%, and the difference was not statistically significant (Table II).

DISCUSSION

Patients aged 50 years or under comprised 35% of all patients in this series, and this constituted a significant proportion. In this group, the tumors were more advanced in stage with more venous permeation, more liver invasion, and of larger size. In addition, there was also less tumor encapsulation. It has been shown that permeation of the portal vein by the tumor is a prognostic factor associated with a poorer patient survival [11] and a higher tumor recurrence rate in the liver remnant [12], particularly associated with a widespread multinodular recurrence [13]. Similarly, absence of tumor encapsulation has been identified to be associated with a shorter disease-free period after resection [14,15].

In this study, the tumors in the younger group were significantly larger in size than those in the older one. This was similar to the findings in other studies, in spite of different cut-off ages (70 and 60 yr) used in two different series [16,17]. In addition, the younger patients in our series also were less often cirrhotic, in accord with the finding in another study that younger patients more frequently had larger tumors and less cirrhosis [17]. In resected HCCs, the tumors in cirrhotic patients were significantly smaller than those in noncirrhotic livers [18,19]. This could have been due to the selection of patients with good hepatocellular reserves for surgical resection, but tumor size also has been reported to be larger in noncirrhotic patients than in cirrhotic ones in unselected patients using ultrasonography combined with computed tomography and angiography [20]. Further study is required to delineate the relationship between cirrhosis and tumor size.

The patients in the younger group were more frequently HBsAg positive and less frequently cirrhotic. The cirrhosis, if present, was more often inactive. In another study, patients <45 years of age also showed a higher incidence of HBsAg positivity and a low incidence of histologically confirmed cirrhosis [5]. The HCC in the young and old groups may have different etiologic factors. In Hong Kong and Southeast Asia, chronic hepatitis B virus infection due to vertical transmission of the virus at and around the time of birth is a major etiologic factor in young patients with HCC. However, a higher positive rate for hepatitis C virus antibody has been reported in the older patients [7], and this probably indicates a different etiologic role in different age groups.

In HCC, some studies showed that patients with younger age had a better survival than older patients after tumor resection [1–3,11] or when treated with systemic chemotherapy [21]. However, our results in this study demonstrated a lack of significant influence of age on survival rates, using an age of 50 years for stratification. The age of 50 years was chosen as a cutoff point because it was closest to the mean age (53 years) of all patients analyzed, and a round-off figure to the nearest decade is more practical in clinical practice. We also compared the survival of patients stratified according to decades of age (youngest to 40 yr, 41–50 yr, 51–60, and 60 to oldest) but did not find a significant difference in survival lengths. The mortality and disease recurrence in patients older than 50 years were not prohibitive after major hepatectomy for HCC and were comparable to those in younger patients. Several other groups also found a lack of relationship between patient age and survival rates in those with resected HCCs [5,7,16,22], although some of them used a different cutoff age of 70 years [5,7,16]. In addition to survival rates, Nagasue et al. [6] found similar resectability and hospital mortality rates between those older than 70 years and those younger than 50.

A higher preoperative serum AFP level was seen in the younger group, with 72.6% of patients having an AFP level >200 ng/ml, compared to 58.8% in the older group. A higher serum AFP level has been shown to be associated with a shorter long-term survival [2,23,24] and sooner recurrence [25] in patients with HCC after surgical resection. A higher AFP level is also an adverse prognos-

tic factor in patients with unresectable HCC treated with transcatheter arterial embolization [26,27], and a factor related to ineffectiveness of systemic chemotherapy [28].

It is intriguing, however, to find that with all these adverse factors in the younger patients, namely, more advanced and less frequently encapsulated tumors and a higher serum AFP level, the survival rates were similar to those of the older group. The survival rates in the younger patients partly could have been influenced by the fact that these patients were less frequently cirrhotic. Cirrhosis is a major determining factor in selecting patients for surgical resection, and major hepatectomy is considered by some to be contraindicated for hepatocellular carcinoma in patients with cirrhosis because of the high incidence of intraoperative bleeding and postoperative liver failure [29]. Moreover, a higher intrahepatic tumor recurrence rate is also seen in patients with cirrhosis after resection [12]. This could be due to the possibility that cirrhotic livers may contain more foci of multicentric tumors, or that cirrhosis itself predisposes to the development of new HCCs in the liver remnant.

In conclusion, we found that there were distinct differences in the clinical and pathologic features of the tumors between patients older than 50 years and those under. Although the tumors were more advanced in the younger group, the patients were less frequently cirrhotic, and this might have partly compensated to result in similar survival rates. Because of the similar survival in the older group, the treatment policy should not differ greatly from that in the younger group.

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